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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,077	SMALL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *23-29 and 45-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,30-44 and 63* is/are rejected.

7)☒ Claim(s) *20 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *GenBank Record AF009500*.

DETAILED ACTION

1. The examiner handling this application has changed. Please address future correspondence to Juliet Switzer, Art Unit 1634.

2. Applicant's amendments and arguments set forth in the response filed 9/16/04 have been considered but are not sufficient to place the claims in condition for allowance. New grounds of rejection are set forth in this office action. Any outstanding rejection that is not reiterated herein is WITHDRAWN. Applicant's remarks are addressed throughout the office action, as appropriate.

3. Claims 1-63 are pending. Claims 23-29 and claims 45-62 are withdrawn from prosecution as being drawn to non-elected subject matter.

Specification

4. The disclosure is objected to because of the following informalities:

At page 14 of the specification applicant states that GenBank record AF009500 is contains the sequence of the gene encoding α2B-adrenergic receptor. However, this GenBank record contains the Streptococcus suis 16S ribosomal RNA gene, complete sequence (see enclosed GenBank Record). There is a clear inconsistency.

At page 15 of the specification, it is taught that instant SEQ ID NO: 5 is the complement of instant SEQ ID NO: 3. However, this is not accurate. Rule 1.822(c)(5) requires that the nucleic acids in a sequence listing are provided in the 5' to 3' direction, from left to right. Thus, given in the sequence listing is SEQ ID NO: 3: 5'-gaagaggag-3'. The complement of this molecule, written 5' to 3' is 5'-ctcctcttc-3', NOT 5'-cttctcctc-3' as set forth in SEQ ID NO: 5 and in the specification at page 15. For the same reason, instant SEQ ID NO: 6 is not the

complement of instant SEQ ID NO: 4. Correction is required, including if necessary new paper and electronic copies of the CRF and appropriate papers necessary to comply with the sequence rules.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter. The amended claims recite an oligonucleotide "comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2." The specification does not appear to provide basis for a nucleotide sequence that is "homologous" to this region since homology could include mismatched sequences, for example. No basis for this amendment was identified in the response and a review of the specification by the examiner did not result in the identification of basis for the amendment. Therefore, the claims are rejected for the inclusion of new matter.

Claim Objections

7. Claims 20 and 30 are objected to because of the following informalities:

In claim 20 there is a period in the middle of the word "chemiluminescent." This appears to be a typographical error.

In claim 30 part (a) there is not a space between "a" and "polynucleotide." This appears to be a typographical error.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-5, 8-11, 13-15, 18, 33-36, and 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite because it is not clear what it means for a "polymorphism" to comprise a particular sequence. As defined in the specification, a "polymorphism" exists when there is variation between some members of a species. Therefore, a "polymorphism" exists when there are two possible versions of a sequence present in a population. In the claim, however, applicant appears to be referring to "versions" of a polymorphism, commonly referred to as alleles. Thus, the polymorphism itself cannot comprise a sequence since it is not a molecule, but a variation between two molecules. The claim would be clearer if it recited, for example, "wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or the complement thereof, at the polymorphic site."

Claim 3 is indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." The claim is not clear because it does not set forth what the insertion is relative to. Instant SEQ ID NO: 1 contains the sequence "wild type" molecule, which has all of the nucleotides in tact. The claim as written appears to require that the polymorphism to be detected includes in insertion into instant SEQ ID NO: 1. However, this is not consistent with the specification which teaches that the two alleles of the polymorphism that is the object of applicant's invention are either SEQ ID NO: 1 or SEQ ID NO: 2 and that SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. By extension, therefore, instant SEQ ID NO: 1 has an insertion relative to SEQ ID NO: 2. However, this polymorphism is not what the claim appears to set forth since the claim requires an insertion of 9 nucleotides into SEQ ID NO: 1. Therefore, it is not clear if the insertion is into to SEQ ID NO: 1, that is, to add an additional nine nucleotides somewhere within positions 901-909 of SEQ ID NO: 1, or if the insertion is relative to SEQ ID NO: 2 and SEQ ID NO: 1 is the example of the full length sequence which contains the insertion. Further, as noted in the previous office action, the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this region, replacement of these 9 nucleotides with 9 different nucleotides, etc. Amendment of the claim to recite, for example, "wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2, wherein the sequence is inserted immediately after position 900 of SEQ ID NO: 2" would clarify this claim.

Claim 4 is indefinite for reasons analogous to claim 3. The claim requires that the "polymorphism is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO:

2." Instant SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. It is not clear if the claim is requiring an additional deletion of nine nucleotides from SEQ ID NO: 2 as it is recited or if the claim intends to recite that the sequence with the deletion is SEQ ID NO: 2. Amendment of the claim to recite, for example, "wherein the polymorphism is deletion of nine nucleotides from SEQ ID NO: 1, wherein the deleted sequence is nucleotides 901 to 909 of SEQ ID NO: 1" would clarify this claim.

Claim 5 are indefinite because SEQ ID NO: 5 and SEQ ID NO: 6 are not the complement of SEQ ID NO: 3 or SEQ ID NO: 4. Rule 1.822(c)(5) requires that the nucleic acids in a sequence listing are provided in the 5' to 3' direction, from left to right. Thus, given in the sequence listing is SEQ ID NO: 3: 5'-gaagaggag-3'. The complement of this molecule, written 5' to 3' is 5'-ctcctcttc-3', NOT 5'-cttctcctc-3' as set forth in SEQ ID NO: 5 and in the specification at page 15. For the same reason, instant SEQ ID NO: 6 is not the complement of instant SEQ ID NO: 4.

Claim 8 is indefinite because it is not clear what it means for a "polymorphism" to comprise a particular sequence. As defined in the specification, a "polymorphism" exists when there is variation between some members of a species. Therefore, a "polymorphism" exists when there are two possible versions of a sequence present in a population. In the claim, however, applicant appears to be referring to "versions" of a polymorphism, commonly referred to as alleles. Thus, the polymorphism itself cannot comprise a sequence since it is not a molecule, but a variation between two molecules. The claim would be clearer if it recited, for example, "wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or the complement thereof, at the polymorphic site."

Claim 9 is indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." The claim is not clear because it does not set forth what the insertion is relative to. Instant SEQ ID NO: 1 contains the sequence "wild type" molecule, which has all of the nucleotides in tact. The claim as written appears to require that the polymorphism to be detected includes in insertion into instant SEQ ID NO: 1. However, this is not consistent with the specification which teaches that the two alleles of the polymorphism that is the object of applicant's invention are either SEQ ID NO: 1 or SEQ ID NO: 2 and that SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. By extension, therefore, instant SEQ ID NO: 1 has an insertion relative to SEQ ID NO: 2. However, this polymorphism is not what the claim appears to set forth since the claim requires an insertion of 9 nucleotides into SEQ ID NO: 1. Therefore, it is not clear if the insertion is into to SEQ ID NO: 1, that is, to add an additional nine nucleotides somewhere within positions 901-909 of SEQ ID NO: 1, or if the insertion is relative to SEQ ID NO: 2 and SEQ ID NO: 1 is the example of the full length sequence which contains the insertion. Further, as noted in the previous office action, the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this region, replacement of these 9 nucleotides with 9 different nucleotides, etc. Amendment of the claim to recite, for example, "wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2, wherein the sequence is inserted immediately after position 900 of SEQ ID NO: 2" would clarify this claim.

Claim 10 is indefinite for reasons analogous to claim 9. The claim requires that the "polymorphism is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO:

2." Instant SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. It is not clear if the claim is requiring an additional deletion of nine nucleotides from SEQ ID NO: 2 as it is recited or if the claim intends to recite that the sequence with the deletion is SEQ ID NO: 2. Amendment of the claim to recite, for example, "wherein the polymorphism is deletion of nine nucleotides from SEQ ID NO: 1, wherein the deleted sequence is nucleotides 901 to 909 of SEQ ID NO: 1" would clarify this claim.

Claim 11 is indefinite because SEQ ID NO: 5 and SEQ ID NO: 6 are not the complement of SEQ ID NO: 3 or SEQ ID NO: 4. Rule 1.822(c)(5) requires that the nucleic acids in a sequence listing are provided in the 5' to 3' direction, from left to right. Thus, given in the sequence listing is SEQ ID NO: 3: 5'-gaagaggag-3'. The complement of this molecule, written 5' to 3' is 5'-ctcctcttc-3', NOT 5'-cttctcctc-3' as set forth in SEQ ID NO: 5 and in the specification at page 15. For the same reason, instant SEQ ID NO: 6 is not the complement of instant SEQ ID NO: 4.

Claims 13-15 are indefinite over the language "employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof." The claim is confusing because it requires "at least one nucleotide" (so as few as one) but that the "at least one" comprise a sequence which would be more than one nucleotide. It is not clear what applicant is trying to say about the oligonucleotide.

Claim 18 is indefinite over the inclusion of SEQ ID Nos 17-18 in the claim. It is noted that claim 16 requires an oligonucleotide "having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the

identification of the nucleotide present at a polymorphic site of the polynucleotide." However, SEQ ID Nos 17-18 are identified in the specification as being primers that specifically hybridize to M13 vectors, not to a "polymorphic site" within the polynucleotide of the instant claims. Thus, it is unclear as to how or whether SEQ ID Nos 17-18 might function in the methods of the claims as presently written.

Claim 33 is indefinite because it is not clear what it means for a "polymorphism" to comprise a particular sequence. As defined in the specification, a "polymorphism" exists when there is variation between some members of a species. Therefore, a "polymorphism" exists when there are two possible versions of a sequence present in a population. In the claim, however, applicant appears to be referring to "versions" of a polymorphism, commonly referred to as alleles. Thus, the polymorphism itself cannot comprise a sequence since it is not a molecule, but a variation between two molecules. The claim would be clearer if it recited, for example, "wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or the complement thereof, at the polymorphic site."

Claim 34 is indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." The claim is not clear because it does not set forth what the insertion is relative to. Instant SEQ ID NO: 1 contains the sequence "wild type" molecule, which has all of the nucleotides in tact. The claim as written appears to require that the polymorphism to be detected includes in insertion into instant SEQ ID NO: 1. However, this is not consistent with the specification which teaches that the two alleles of the polymorphism that is the object of applicant's invention are either SEQ ID NO: 1 or SEQ ID NO: 2 and that SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. By

extension, therefore, instant SEQ ID NO: 1 has an insertion relative to SEQ ID NO: 2. However, this polymorphism is not what the claim appears to set forth since the claim requires an insertion of 9 nucleotides into SEQ ID NO: 1. Therefore, it is not clear if the insertion is into to SEQ ID NO: 1, that is, to add an additional nine nucleotides somewhere within positions 901-909 of SEQ ID NO: 1, or if the insertion is relative to SEQ ID NO: 2 and SEQ ID NO: 1 is the example of the full length sequence which contains the insertion. Further, as noted in the previous office action, the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this region, replacement of these 9 nucleotides with 9 different nucleotides, etc. Amendment of the claim to recite, for example, "wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2, wherein the sequence is inserted immediately after position 900 of SEQ ID NO: 2" would clarify this claim.

Claim 35 is indefinite for reasons analogous to claim 34. The claim requires that the "polymorphism is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2." Instant SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. It is not clear if the claim is requiring an additional deletion of nine nucleotides from SEQ ID NO: 2 as it is recited or if the claim intends to recite that the sequence with the deletion is SEQ ID NO: 2. Amendment of the claim to recite, for example, "wherein the polymorphism is deletion of nine nucleotides from SEQ ID NO: 1, wherein the deleted sequence is nucleotides 901 to 909 of SEQ ID NO: 1" would clarify this claim.

Claim 36 are indefinite because SEQ ID NO: 5 and SEQ ID NO: 6 are not the complement of SEQ ID NO: 3 or SEQ ID NO: 4. Rule 1.822(c)(5) requires that the nucleic acids

in a sequence listing are provided in the 5' to 3' direction, from left to right. Thus, given in the sequence listing is SEQ ID NO: 3: 5'-gaagaggag-3'. The complement of this molecule, written 5' to 3' is 5'-ctcctcttc-3', NOT 5'-cttctcctc-3' as set forth in SEQ ID NO: 5 and in the specification at page 15. For the same reason, instant SEQ ID NO: 6 is not the complement of instant SEQ ID NO: 4.

Claim 40 is indefinite because it is not clear what it means for a "polymorphism" to comprise a particular sequence. As defined in the specification, a "polymorphism" exists when there is variation between some members of a species. Therefore, a "polymorphism" exists when there are two possible versions of a sequence present in a population. In the claim, however, applicant appears to be referring to "versions" of a polymorphism, commonly referred to as alleles. Thus, the polymorphism itself cannot comprise a sequence since it is not a molecule, but a variation between two molecules. The claim would be clearer if it recited, for example, "wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or the complement thereof, at the polymorphic site."

Claim 41 is indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." The claim is not clear because it does not set forth what the insertion is relative to. Instant SEQ ID NO: 1 contains the sequence "wild type" molecule, which has all of the nucleotides in tact. The claim as written appears to require that the polymorphism to be detected includes in insertion into instant SEQ ID NO: 1. However, this is not consistent with the specification which teaches that the two alleles of the polymorphism that is the object of applicant's invention are either SEQ ID NO: 1 or SEQ ID NO: 2 and that SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. By

extension, therefore, instant SEQ ID NO: 1 has an insertion relative to SEQ ID NO: 2. However, this polymorphism is not what the claim appears to set forth since the claim requires an insertion of 9 nucleotides into SEQ ID NO: 1. Therefore, it is not clear if the insertion is into to SEQ ID NO: 1, that is, to add an additional nine nucleotides somewhere within positions 901-909 of SEQ ID NO: 1, or if the insertion is relative to SEQ ID NO: 2 and SEQ ID NO: 1 is the example of the full length sequence which contains the insertion. Further, as noted in the previous office action, the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this region, replacement of these 9 nucleotides with 9 different nucleotides, etc. Amendment of the claim to recite, for example, "wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2, wherein the sequence is inserted immediately after position 900 of SEQ ID NO: 2" would clarify this claim.

Claim 42 is indefinite for reasons analogous to claim 41. The claim requires that the "polymorphism is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2." Instant SEQ ID NO: 2 has a deletion relative to SEQ ID NO: 1. It is not clear if the claim is requiring an additional deletion of nine nucleotides from SEQ ID NO: 2 as it is recited or if the claim intends to recite that the sequence with the deletion is SEQ ID NO: 2. Amendment of the claim to recite, for example, "wherein the polymorphism is deletion of nine nucleotides from SEQ ID NO: 1, wherein the deleted sequence is nucleotides 901 to 909 of SEQ ID NO: 1" would clarify this claim.

Claim 43 are indefinite because SEQ ID NO: 5 and SEQ ID NO: 6 are not the complement of SEQ ID NO: 3 or SEQ ID NO: 4. Rule 1.822(c)(5) requires that the nucleic acids

in a sequence listing are provided in the 5' to 3' direction, from left to right. Thus, given in the sequence listing is SEQ ID NO: 3: 5'-gaagaggag-3'. The complement of this molecule, written 5' to 3' is 5'-ctcctcttc-3', NOT 5'-cttctcctc-3' as set forth in SEQ ID NO: 5 and in the specification at page 15. For the same reason, instant SEQ ID NO: 6 is not the complement of instant SEQ ID NO: 4.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-14, 16-17, 20-22, 31-44, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Heinonen (The Journal of Clinical Endocrinology & Metabolism, July 1999, as cited in the IDS).

Heinonen et al. teach a deletion of nine nucleotides in frame of the alpha-2B-adrenergic receptor molecule that results in the loss of three glutamatic acid residues from the encoded polypeptide (see Figure 1 of Heinonen et al.). The sequence deleted is identical to instant SEQ ID NO: 3. Further, the instant specification teaches that the deletion taught in this reference is identical to the deletion identified in this application (see p. 58, line 10). Heinonen et al. teach taht the deletion polymorphism is associated with reduced BMR in obese, non-diabetic Finns (p. 2431). Heinonen et al. suggest a possible mechanistic explanation for the association is related

to possible incapability of the encoded deletion polypeptide of being phosphorylated and desensitized in the normal manner (p. 2431, final ¶).

With regard to claim 1, Heinonen et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 2430);

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 2430, PCR-SSCA analysis, Sequencing and genotyping, and Figure 1).

The preamble of claim 1 recites a method of determining alpha-2B-adrenergic receptor function by detecting a polymorphism at a polymorphic site. The claim does not, however, contain any method steps which relate the detecting of a polymorphic site to the determination of alpha-2B-adrenergic receptor function, per se. The teachings of Heinonen et al. provide the manipulative method steps recited in claim 1.

With regard to claim 6, Heinonen et al. teach a method comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 2430);

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 2430, PCR-SSCA analysis, Sequencing and genotyping, and Figure 1).

With regard to claim 31, Heinonen et al. teach a method of identifying an individual increased risk for developing a disease associated with alpha-2B-adrenergic receptor molecule comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide from the individual (p. 2430); and

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of positions 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof, wherein the polymorphism correlates to the disease (p. 2430), thereby identifying the individual at risk for the disease. Namely, Heinonen et al. teach that alleles of the polymorphism are associated with reduced basal metabolic rate in obese subjects, and by extension that the alleles are a predictor of an increased risk of developing obesity (abstract and throughout, especially p. 2432).

With regard to claim 38, Heinonen et al. teach a method which comprises the steps of:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide from the individual (p. 2430); and

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of positions 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof, wherein the polymorphism correlates to the disease (p. 2430). Namely, Heinonen et al. teach that alleles of the polymorphism are associated with reduced basal metabolic rate in obese subjects, and by extension that the alleles are a predictor of an increased risk of developing obesity (abstract and throughout, especially p. 2432). With regard to the language of the preamble, reciting "a method

for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule," Heinonen et al. are considered to inherently meet this step as they meet all of the structural limitations of the claim as recited.

With regard to claims 32 and 39, Heinonen et al. teach determining a predisposition to obesity, which by extension suggests an increased likelihood of a wide variety of cardiovascular diseases that are related to obesity.

With regard to claims 2, 8, 33, and 40 both versions of the alpha-2B-adrenergic receptor sequence contain both SEQ ID NO: 3 and SEQ ID NO: 4, see Figure 1.

With regard to claims 3, 9, 34, and 41, Heinonen et al. teach an insertion of 9 nucleotides in the long form relative to the short form.

With regard to claims 4, 10, 35, and 42, Heinonen et al. teach a deletion of 9 nucleotides in the short form relative to the long form.

With regard to claims 5, 11, 36, and 43, the complement of the polymorphism (i.e. the deleted portion) is 5'-ctcctcttc-3', which is the REVERSE of SEQ ID NO: 5 (see 112 2nd rejection herein).

With regard to claim 7, Heinonen et al. genotype two copies of the gene for all patients (p. 2430).

With regard to claims 12, Heinonen et al. teach single-stranded conformational polymorphism analysis using restriction digestion for detection of the polymorphism (p. 2430).

With regard to claim 37 and 44,the alpha-2B-adrenergic receptor molecule inherently comprises SEQ ID NO: 7 or SEQ ID NO: 8, as well as "a fragment thereof" which can be as few

as a single amino acid. All polypeptide sequences comprise a fragment of SEQ ID NO: 7 or SEQ ID NO: 8 given the plain language of the claim.

With regard to claim 13, Heinonen et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. Specifically, Heinonen et al. perform a PCR reaction (which is a primer extension reaction) that utilizes a primer that comprises sequence "GAA" which is identical to a nucleotide sequence located between positions 901 to 909 of SEQ ID NO: 1 (see the second primer recited in "pair 2" in the 1st column of p. 2430). The claim requires only that the primer "comprise at least one nucleotide" that comprises a sequence with homology (any level of homology) to the nucleotides within SEQ ID NO: 1. The primer taught by Heinonen et al. meet this limitation.

With regard to claim 14, the oligonucleotide has nineteen nucleotides.

With regard to claim 16, the PCR methods taught by Heinonen et al. also meet the limitations of these claims. Referring in particular to part (b) of the claim, Heinonen et al. teach subjecting a polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a nucleotide sequence that is complementary to a region of SEQ ID NO: 1 and SEQ ID NO: 2, and when hybridized the region permits the identification of the nucleotide present at a polymorphic site of a polynucleotide (p. 2430, PCR-SSCA analysis, and Sequencing and Genotyping, for example). The hybridization of the primers used by Heinonen et al. permit the identification of the polynucleotide because they are used in an assay to identify the

polymorphism. Heinonen et al. permit hybridization to occur, and identify the polymorphic site to obtain the gentoype of the individual. The polymorphism detected by Heinonen et al. is an insertion or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2.

With regard to claim 17, Heinonen et al. teach multiple rounds of PCR, and thus, teach amplification prior to hybridization (i.e. amplification in a round of PCR prior to a particular hybridization of primers in a later round).

With regard to claim 20, the oligonucleotides themselves have sequences which are nucleic acid labels.

With regard to claim 21, Heinonen et al. use restriction digestion to determine the identity of the polymorphic site.

With regard to claim 22, the primers used by Heinonen et al. are all between 10 and 50 nucleotides in length.

With regard to claim 63, Heinonen et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 2430);

b. indirectly detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 2430, PCR-SSCA analysis, Sequencing and genotyping, and Figure 1).

The preamble of claim 1 recites a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site. The claim does not,

however, contain any method steps which relate the detecting of a polymorphic site to the determination of alpha-2B-adrenergic receptor function, per se. The teachings of Heinonen et al. provide the manipulative method steps recited in claim 63. Heinonen et al. "indirectly" detect the allele present at the polymorphic site via the size of fragments on an electrophoresis gel.

12. Claims 1-6, 8-13, 16, 20-21, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Jewell-Motz (Biochemistry, 1995, Vol. 34, pages 11946-11953, as cited in the IDS).

Jewell-Motz et al. used site-directed mutagenesis to delete or substitute a 16 amino acid stretch of glutamic acid residues from the alpha-2B-adrenergic receptor molecule (see Figure 1 of Jewell-Motz et al.). The sequence deleted inherently would include instant SEQ ID NO: 3 which encodes three glutamic acid residues within a 16 amino acid repeat sequence of glutamic acids in the alpha-2B-adrenergic receptor molecule. Jewell-Motz et al. teach that the deletion of and substitution of this section results in receptors that undergo agonist-promoted phosphorylation at levels of only about 44 and 50%, respectively, relative to wild type. Jewell-Motz et al. teach that after the site-directed mutagenesis of the nucleic acid encoding the wild-type alpha-2B-adrenergic receptor molecule, presence of the mutations were detected using nucleotide tracking and sequencing. Further, they teach that final constructs were analyzed using restriction analysis and sequencing to confirm the presence of the desired mutation.

Thus, with regard to claim 1, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 11947).

The preamble of claim 1 recites a method of determining alpha-2B-adrenergic receptor function by detecting a polymorphism at a polymorphic site. The claim does not, however, contain any method steps which relate the detecting of a polymorphic site to the determination of alpha-2B-adrenergic receptor function, per se. The teachings of Jewell-Motz et al. provide the manipulative method steps recited in claim 1, as the mutations detected by Jewell-Motz et al. would comprise all of nucleotide positions 901-909 of SEQ ID NO: 1 and SEQ ID NO: 2, either as a deletion or as substituted nucleotides. The mutations detected by Jewell-Motz et al. include additional nucleotides relative to these positions, but the claims are drawn using broad langage and encompass detection of larger "polymorphic" regions, as detected by Jewell-Motz et al. Further, Jewell-Motz et al. teach the effects of these mutations on receptor function.

With regard to claim 6, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p.11947).

With regard to claims 2 and 8, the claims require only that the polymorphism comprise "a complement" of SEQ ID NO: 3 or SEQ ID NO: 4. The phrase "a complement" is interpreted to include any molecules that contain at least a single nucleotide that is "a complement" of any portion of SEQ ID NO: 3 and SEQ ID NO: 4. The substitution mutant provided by Jewell-Motz et al. encodes a segment of glutamines which are encoded by "CCA" or "CAG", which include "a complement" of SEQ ID NO: 3 since "C" is a complement of "G."

With regard to claims 3, 4, 9 and 10, in Jewell-Motz et al. the wild type teach an insertion of 9 nucleotides (plus additional nucleotides) relative to the deletion mutant.

With regard to claims 4 and 10, Jewell-Motz et al. teach a deletion of 9 nucleotides relative to the wild type.

With regard to claims 5 and 11, the complement of the deleted portion contains a deletion that is the complement of 5'-ctcctcttc-3', which is the REVERSE of SEQ ID NO: 5 (see 112 2nd rejection herein).

With regard to claims 12, Jewell-Motz et al. teach restriction digestion for detection of the polymorphism (p. 11947).

With regard to claim 13, Jewell-Motz et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide

sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. Specifically, Jewell-Motz et al. perform a sequencing reaction (which is a primer extension reaction) that would inherently have included the use of extended oligonucleotides that overlap with the polymorphic position. Jewell-Motz et al. do not give the sequence of the sequencing primers, but sequencing would have required the extension of primers. The claim requires only that the primer "comprise at least one nucleotide" that comprises a sequence with homology (any level of homology) to the nucleotides within SEQ ID NO: 1. The primer inherently used by Jewell-Motz et al. meet this limitation.

With regard to claim 16, the sequencing methods taught by Jewell-Motz et al. also meet the limitations of these claims. Referring in particular to part (b) of the claim, Jewell-Motz et al. teach sequencing the mutant polynucleotides which would have required subjecting a polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a nucleotide sequence that is complementary to a region of SEQ ID NO: 1 and SEQ ID NO: 2, and when hybridized the region permits the identification of the nucleotide present at a polymorphic site of a polynucleotide (p. 11947). The hybridization of the primers used by Jewell-Motz et al. permit the identification of the polynucleotide because they are used in an assay to identify the polymorphism. Jewell-Motz et al. permit hybridization to occur, and identify the polymorphic site to obtain the gentoype of the individual. The polymorphism detected by Jewell-Motz et al. is an insertion or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2.

With regard to claim 20, the oligonucleotides themselves have sequences which are nucleic acid labels.

With regard to claim 21, Jewell-Motz et al. use restriction digestion to determine the identity of the polymorphic site.

With regard to claim 63, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 2430);

b. indirectly detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 2430, PCR-SSCA analysis, Sequencing and genotyping, and Figure 1).

The preamble of claim 1 recites a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site. The claim does not, however, contain any method steps which relate the detecting of a polymorphic site to the determination of alpha-2B-adrenergic receptor function, per se. The teachings of Jewell-Motz et al. provide the manipulative method steps recited in claim 63. Jewell-Motz et al. "indirectly" detect the allele present at the polymorphic site via restriction digestion.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heinonen et al. in view of Shuber et al. (6566101).

With regard to claim 13, from which claim 13 depends, Heinonen et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. Specifically, Heinonen et al. perform a PCR reaction (which is a primer extension reaction) that utilizes a primer that comprises sequence "GAA" which is identical to a nucleotide sequence located between positions 901 to 909 of SEQ ID NO: 1 (see the second primer recited in "pair 2" in the 1st column of p. 2430). The claim requires only that the primer "comprise at least one nucleotide" that comprises a sequence with homology (any level of homology) to the nucleotides within SEQ ID NO: 1. The primer taught by Heinonen et al. meet this limitation.

Heinonen et al. do not teach a method wherein the primer extension is a single nucleotide extension as required by instant claim 15. Shuber et al. teach primer extension methods for detecting nucleic acids which employ single nucleotide extension. Shuber et al. specifically suggest that their methods can be applied to the detection of mutations in samples, particularly suggesting the detection of deletions (Col. 6, lines 24-46, for example).

Thus, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method taught by Heinonen et al. so as to have utilized the detection methods taught by Shuber et al. to detect the deletion taught by Heinonen et al. One would have been motivated to use the methods taught by Shuber et al. to obtain the express benefits of the method as taught by Shuber et al. who state "The present invention is the first to provide a single base extension assay with both high selectivity and high sensitivity (Col. 8, lines 40-41)...Methods of the invention are useful to detect and identify mutations associated with diseases such as cancer, deletions or a base substitution mutations causative of a metabolic error, such as complete or partial loss of enzyme activity, portions of a particular gene or genetic locus in the patient's genomic nucleic acid known to be involved in a pathological condition or syndrome....(Col. 8, lines 53-60)." Thus in view of the prior art, the claimed invention is prima facie obvious.

16. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heinonen et al. in view of Baldwin et al (American Journal of Hypertension 12:853-857 [9/1999], as cited in IDS) and Newton ("Chapter 6: Primers," in *PCR Essential Data*, C.R. Newton, ed., John Wiley & Sons, Chichester, 1995, pages 49-56, cited in previous office action).

With regard to claim 16, from which claim 18 depends, Heinonen et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. Specifically, Heinonen et al. perform a PCR reaction (which is a primer extension reaction) that utilizes a primer that comprises sequence "GAA" which is identical to a nucleotide sequence located between positions 901 to 909 of SEQ ID NO: 1 (see the second primer recited in "pair 2" in the 1st column of p. 2430). The PCR methods taught by Heinonen et al. meet the limitations of claim 16. Referring in particular to part (b) of the claim, Heinonen et al. teach subjecting a polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a nucleotide sequence that is complementary to a region of SEQ ID NO: 1 and SEQ ID NO: 2, and when hybridized the region permits the identification of the nucleotide present at a polymorphic site of a polynucleotide (p. 2430, PCR-SSCA analysis, and Sequencing and Genotyping, for example). The hybridization of the primers used by Heinonen et al. permit the identification of the polynucleotide because they are used in an assay to identify the polymorphism. Heinonen et al. permit hybridization to occur, and identify the polymorphic site to obtain the gentoype of the individual. The polymorphism detected by Heinonen et al. is an insertion or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2.

Heinonen et al. do not teach a method wherein the at least one oligonucleotide is SEQ ID NO: 13.

Baldwin et al disclose a method of detecting polymorphisms in the human I_{2B}-AR gene in which overlapping fragments of the gene are sequenced, and in which the same variant sequence disclosed by Baldwin et al. is detected (see entire reference, particularly page 854, right column-page 855, left column; and Table 1). The primers employed by Baldwin et al in sequencing include primer 1311 (see Table 1); nucleotides 1-19 of primer 1311 are the complement of nucleotides 1-19 of instant SEQ ID NO: 13. Accordingly, instant SEQ ID NO: 13 targets the same region of the human I_{2B}-AR gene sequence as the primer of Baldwin et al, but on the opposite strand. Baldwin et al further disclose that primer 1311 hybridizes at nucleotide 619 of the human I_{2B}-AR gene, and thus is located 5' of the polymorphism taught by both Baldwin et al and Heinonen et al. Newton et al teach the design of primers for PCR, providing guidance with respect to desirable characteristics as well as properties to avoid when designing PCR primer pairs (see entire reference, particularly pages 50-51).

In view of the teachings of Baldwin et al, and given the guidance provided by Newton regarding the design of PCR primers, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Heinonen et al so as to have employed therein a variety of different primers, including a primer consisting of instant SEQ ID NO: 13. One would have been motivated to provide additional means for the amplification of the sequence surrounding the mutation taught by Heinonen et al., and would have been motivated by the teachings of Baldwin et al. to target a region of the gene that was successfully targeted for amplification in previous assays. As Baldwin et al disclose that the region of their primer 1311/instant SEQ ID NO: 13 may be successfully targeted in PCR amplification, an ordinary artisan would have been motivated to have selected primers that

hybridize specifically to this region (including a primer consisting of SEQ ID NO: 13), rather than to have experimented to identify other regions suitable for primer hybridization, for the advantages of convenience and efficiency providing additional primers for the amplification of the region containing the mutation taught by Heinonen et al. Absent a showing of unexpected results with the particular sequence of the claim, any primers targeting the region suggested by Baldwin et al and meeting the criteria of Newton would be obvious over Henionen et al in view of Baldwin et al and Newton. It is further noted that as SEQ ID NO: 13 meets the desired criteria disclosed by Newton for length, melting temperature, GC content, etc., an ordinary artisan would have had a reasonable expectation of success in employing this primer, as well as a variety of other primers suggested by the references, in the method of Heinonen et al.

17. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heinonen et al. in view of Snapir et al.

With regard to claim 16, from which claim 19 depends, Heinonen et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. Specifically, Heinonen et al. perform a PCR reaction (which is a primer extension reaction) that utilizes a primer that comprises sequence "GAA" which is identical to a nucleotide sequence located between positions 901 to 909 of SEQ ID NO: 1 (see the second primer recited in "pair 2" in the 1st column of p. 2430). The PCR methods taught by

Heinonen et al. meet the limitations of claim 16. Referring in particular to part (b) of the claim, Heinonen et al. teach subjecting a polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a nucleotide sequence that is complementary to a region of SEQ ID NO: 1 and SEQ ID NO: 2, and when hybridized the region permits the identification of the nucleotide present at a polymorphic site of a polynucleotide (p. 2430, PCR-SSCA analysis, and Sequencing and Genotyping, for example). The hybridization of the primers used by Heinonen et al. permit the identification of the polynucleotide because they are used in an assay to identify the polymorphism. Heinonen et al. permit hybridization to occur, and identify the polymorphic site to obtain the gentoype of the individual. The polymorphism detected by Heinonen et al. is an insertion or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2.

Heinonen et al. do not teach a method for detection of the polymorphism using one of the specific hybridization methodologies recited in claim 19.

At the time the invention was made, the detection of genetic variants using any of the recited hybridization methods was routine in the art. Snapir et al. teach methods for detecting a polymorphism within a polynucleotide encoding an alpha-2B-adrenergic receptor molecule, wherein the polymorphism results in a loss of three glutamic acids in the encoded receptor. Snapir et al. teach that the polymorphism can be detected using a variety of routine methods including allele specific probes and northern blot assays (¶ 33). Thus, at the time the invention was made, it would have been prima facie obvious to have modified the methods taught by Heinonen et al. so as to have utilized the hybridization methods taught by Snapir et al. in order to

have provided additional methods for the detection of the polymorphism taught by Heinonen et al.

18. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (American Journal of Medical Genetics, Vol. 81, No. 6, p. 510, Abstract #93) in view of Heinonen et al.

Ho et al. teach a method of haplotyping the a nucleic acid encoding alpha-2B-adrenergic receptor which comprises the detection of a deletion of nine nucleotides and a silant point mutation both of which were found within the third intracellular loop of the receptor gene. Ho et al. teach that for all individual analysed the two polymorphisms were in complete disequilibrium, thus they teach the detection of the two polymorphisms on a first copy of an individual's gene. Ho et al. do not, however, particularly identify the nine nucleotide deletion.

Heinonen et al. teach a deletion of nine nucleotides in frame of the alpha-2B-adrenergic receptor molecule that results in the loss of three glutamatic acid residues from the encoded polypeptide (see Figure 1 of Heinonen et al.). The sequence deleted is identical to instant SEQ ID NO: 3. Further, the instant specification teaches that the deletion taught in this reference is identical to the deletion identified in this application (see p. 58, line 10). Heinonen et al. teach taht the deletion polymorphism is associated with reduced BMR in obese, non-diabetic Finns (p. 2431). Heinonen et al. suggest a possible mechanistic explanation for the association is related to possible incapability of the encoded deletion polypeptide of being phosphorylated and desensitized in the normal manner (p. 2431, final ¶).

With regard to claim 30, Heinonen et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 2430);

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 2430, PCR-SSCA analysis, Sequencing and genotyping, and Figure 1).

Therefore, at time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have detected the particular three nucleotide deletion taught by Heinonen et al. in the methods taught by Ho et al. One would have been motivated to detect the polymorphism taught by Heinonen et al. in order to have further studied the sample taught by Ho et al. to investigate a potential relationship between polymorphisms in the gene encoding the receptor and disease. Therefore, the invention is prima facie obvious.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 31-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are all drawn to methods of identifying an individual at increased risk for developing a disease associated with an alph-2B-adrenergic receptor molecule or methods for

diagnosing or prognosing an individual with a disease associated with an alph-2B-adrenergic receptor molecule, and the methods recite the detection of a particular polymorphism within the gene encoding the receptor. Thus, for the practice of the claimed invention, the nature of the invention requires a knowledge of at least a predictive association between the polymorphism and a disease.

With regard to the disease in question, the scope of the claims is quite broad-encompassing for the independent claims any possible disease that would be "associated with an alph-2B-adrenergic receptor molecule." This encompasses a wide variety of possible diseases since this receptor mediates peripheral vasoconstriction in response to agonist activation. Dependent claims recite "wherein the disease is a cardiovascular disease, central nervous system disease, or combinations thereof."

The specification does not contain a single working example or guidance concerning which diseases are associated with which alleles of this polymorphism.

This art area is highly unpredictable as the determination of an association between a polymorphism and a disease is an empirical endeavor. Ho et al. (Am. J. Med. Genet. 1998) teach that a deletion of nine nucleotides resulting in the deletion of three glutamate amino acids in this gene is not associated with schizophrenia nor to the response to clozapine. Salonen et al. (Circulation, October 2000) teach that men homozygous for the short form of the receptor had 2.5 times the risk of acute coronary event compared with the other two genotypes, but that the polymorphism was not associated with hypertension. Thus, even in populations where the polymorphisms (at least the polymorphism in the encoded polypeptide) is predictive of one cardiovascular disease it may not be predictive of a different disease. Further, once an

association between a phenotype and a polymorphism is identified, it is sometimes contradicted by other studies. Heinonen et al. (J. of Clinical Endocrinology & Metabolism, 1999) teach that subjects homozygous for the short allele had lower basal metabolic rates than those with the long allele. A later study attempted to replicate this finding but found that the short allele was associated with increased metabolic rates, showing an opposite effect in two different populations (Pollin et al. Obesity Research, October 2000). Though some of the prior art provides associations that may be predictive in some diseases in particular populations, the instant specification does not provide specific guidance or support for the detection of any of these. Given the high degree of unpredictability exemplified in the related art, the findings of one group cannot be applied generically.

The practice of the claimed invention would require extensive experimentation in order to determine which diseases are reliably associated with the disclosed polymorphism. Such study would involve the testing of many patient and control populations for the wide variety of disease that are encompassed within the claims.

Thus, having carefully considered all of these factors- given the nature of the invention, the scope of the claims, the lack of working examples or guidance in the specification, the high level of unpredictability for the related art, and the high level of experimentation necessary to practice the claimed invention, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks; Withdrawn rejections

112 2nd paragraph

All 112 2nd rejections which are not specifically addressed are overcome by applicant's amendments to the claims or arguments set forth in the response. New 112 2nd rejections are set forth to address the amendments to the claims which introduced new issues to the claims.

The rejection of claims 1-5 as being indefinite because it is unclear as to whether the claims merely require detection of a polymorphic site, as indicated by the final step of claim 1, or whether the claims require that detection of a polymorphic site determines "alpha-2B-adrenergic receptor function," as recited in the preamble of claim 1 is WITHDRAWN in view of the amendments to claim 1 which makes clear that the method is achieved via the detection of a polymorphism. Likewise the similar rejection is WITHDRAWN for claim 63.

The rejection of claim 18 with regard to SEQ ID NO: 17 and SEQ ID NO: 18 is MAINTAINED. Applicant argues that since these sequences are "universal sequencing primers" they "may behave" as the at least one oligonucleotide sequence having a sequence that is complementary to a region of the polynucleotide (response, p. 23). This is not persuasive, however, because "the polynucleotide" referred to in the claim is "a polynucleotide encoding an alpha-2B adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2," and these sequences are not complementary to the alpha-2B adrenergic receptor molecule recited in the claim.

Art rejections

The art rejections which relied on Snapir et al. as a primary reference are WITHDRAWN in view of applicant's remarks regarding the difference in the polymorphism detected in Snapir et al. and the polymorphism recited in the instant claims. It is noted that by comparison of SEQ ID NO: 1 and SEQ ID NO: 3 in Snapir et al., it is evident that the deleted nucleotide sequence is

5'-gaggaagag-3', this sequence being identical nucleotides 919-927 of SEQ ID NO: 3 of Snapir et al. The deleted sequence in the instant application is 5'-gaagaggag-3', this sequence being identical to nucleotides 901 to 909 of SEQ ID NO: 3 taught by Snapir et al. In both cases the encoded polypeptides are identical, but the resultant short form of the nucleic acid differ in sequence (compare nucleotides 898-921 of instant SEQ ID NO: 2 with the same nucleotides of SEQ ID NO: 1 taught by Snapir et al.). New art rejections are set forth.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

March 30, 2005

1: AF009500 Reports Streptococcus sui...[gi:3323423] Links

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LOCUS       AF009500                1480 bp    DNA     linear   BCT 16-JUL-1998
DEFINITION  Streptococcus suis 16S ribosomal RNA gene, complete sequence.
ACCESSION   AF009500
VERSION     AF009500.1  GI:3323423
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  ORGANISM  Streptococcus suis
            Bacteria; Firmicutes; Lactobacillales; Streptococcaceae;
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REFERENCE   1  (bases 1 to 1480)
  AUTHORS   Chatellier,S., Harel,J., Zhang,Y., Gottschalk,M., Higgins,R.,
            Devriese,L.A. and Brousseau,R.
  TITLE     Phylogenetic diversity of Streptococcus suis strains of various
            serotypes as revealed by 16S rRNA gene sequence comparison
  JOURNAL   Int. J. Syst. Bacteriol. 48 Pt 2, 581-589 (1998)
   PUBMED   9731300
REFERENCE   2  (bases 1 to 1480)
  AUTHORS   Chatellier,S., Harel,J., Zhang,Y., Gottschalk,M., Higgins,R.,
            Devriese,L. and Brousseau,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-JUN-1997) Department of Pathology and Microbiology,
            Faculty of Veterinary Medecine, University of Montreal, 3200,
            Sicotte Ave, Saint-Hyacinthe, Quebec J2S-7C6, CANADA
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      181 cgcatggtag atacttgaaa ggagcaattg cttcactatg agatggacct gcgttgtatt
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      301 atcggccaca ctgggactga gacacggccc agactcctac gggaggcagc agtagggaat
      361 cttcggcaat gggggcaacc ctgaccgagc aacgccgcgt gagtgaagaa ggttttcgga
      421 tcgtaaagct ctgttgtaag agaagaactg tgagaagagt ggaaagtttc tcacttgacg
      481 gtatcttacc agaaagggac ggctaactac gtgccagcag ccgcggtaat acgtaggtcc
      541 cgagcgttgt ccggatttat tgggcgtaaa gcgagcgcag gcggtttgat aagtctgaag
      601 taaaaggctg tggcttaacc atagtacgct ttggaaactg tcaaacttga gtgcagaagg
      661 ggagagtgga attccatgtg tagcggtgaa atgcgtagat atatggagga acaccggtgg
```

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      721 cgaaagcggc tctctggtct gtaactgacg ctgaggctcg aaagcgtggg gagcgaacag
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      841 gggactcagt gccgcagcta acgcattaag cactccgcct ggggagtacg accgcaaggt
      901 tgaaactcaa aggaattgac gggggcccgc acaagcggtg gagcatgtgg tttaattcga
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     1081 ttgggttaag tcccgcaacg agcgcaaccc ctattgttag ttgccatcat tcagttgggc
     1141 actctagcga gactgccggt aataaaccgg aggaaggtgg ggatgacgtc aaatcatcat
     1201 gcccccttatg acctgggcta cacacgtgct acaatggctg gtacaacgag tcgcaagtcg
     1261 gtgacggcaa gctaatctct taaagccagt ctcagttcgg attgtaggct gcaactcgcc
     1321 tacatgaagt cggaatcgct agtaatcgcg gatcagcacg ccgcggtgaa tacgttcccg
     1381 ggccttgtac acaccgcccg tcacaccacg agagtttgta acacccgaag tcggtgaggt
     1441 aacctttaag gagccagccg cctaaggtgg gatagatgat
//
```